American Journal of Medical Genetics 61:21–25 (1996)

Duplication of 7p: Further Delineation of the Phenotype and Restriction of the Critical Region to the Distal Part of the Short Arm

Orit Reish, Susan A. Berry, Gordon Dewald, and Richard A. King

Departments of Pediatrics (O.R., S.A.B., R.A.K.) and Medicine (R.A.K.), and Institute of Human Genetics (S.A.B., R.A.K.), University of Minnesota, Minneapolis, and Cytogenetics Laboratory (G.D.), Mayo Clinic, Rochester, Minnesota

We report on a patient with duplication of 7p15→pter and review the literature. Patients with partial duplication of the distal 7p, including only the distal segment 7p15→pter, have a syndrome comparable to that of patients with a larger or complete duplication of 7p. This suggests that the critical region for the dup(7p) phenotype is restricted to 7p15→pter. The complete clinical phenotype of dup(7)(p15→pter) includes mental retardation, skull anomalies, large anterior fontanel, cardiovascular defects, joint dislocation and contraction, and gastrointestinal and genital defects. Recognition of the clinical spectrum in patients with a smaller duplication of 7p, and the assignment of this critical region, should prove valuable for accurate counseling, prediction of outcome, and further gene mapping.

KEY WORDS: duplication 7p, deletion 20q, phenotype, critical region

INTRODUCTION

Duplication of the short arm of chromosome 7 is a rare chromosome abnormality with only a limited number of cases reported to date. In spite of the fact that the duplicated segment has varied among reported patients, a characteristic phenotype was defined by Milunsky et al. [1989] including psychomotor retardation, dolichocephaly, large anterior fontanel, hypertelorism, large apparently low-set ears, micrognathia, hyperextensible joints subject to dislocation, and a high rate of cardiac septal defects.

Received for publication January 27, 1995; revision received June 6, 1995.

Address reprint requests to Richard A. King, M.D., Ph.D., Departments of Pediatrics and Medicine and the Institute of Human Genetics, University of Minnesota, 420 Delaware St. S.E., Box 485 UMHC, Minneapolis, MN 55455.

We report on an additional patient with duplication 7p15→7pter resulting from a de novo unbalanced translocation 7;20. This patient, along with reports of 7 other patients with an identical duplicated segment [Willner et al., 1977; Berry et al., 1979; Moore et al., 1982; Schmidt and Gillessen-Kaesbach, 1987; Gabarrón et al., 1988; Delicado et al., 1991; Ramer et al., 1991], led us to review all documented cases in an attempt to further delineate the critical region for this syndrome.

CLINICAL REPORT

The proposita was the product of a 41-week gestation to a 28-year-old mother, and a 31-year-old father. This was the first pregnancy of this nonconsanguineous marriage. The pregnancy was uneventful, and cesarean section was performed due to failure to progress during labor, resulting in a 3,360 g girl with Apgar scores of 8^1 and 9^5. Initial examination in the nursery showed multiple congenital anomalies including asymmetric skull, large anterior fontanel, apparently low-set ears, systolic heart murmur, rectoperineal fistula and imperforate anus, left hip dislocation, equinovarus, and clubfeet. The infant had hyperbilirubinemia and thrombocytopenia which resolved. At age 10 days she developed seizures, responsive to phenobarbital.

The results of MRI and CT of the head were normal. An EEG showed asynchrony of activity and seizures in the right parietal region. An echocardiogram demonstrated a patent ductus arteriosus. An ultrasound study of kidneys documented a hyperechoic texture bilaterally, and an elongated bladder was noted on a voiding cystourethrogram. An auditory brain response using click thresholds showed combined neural and conductive hearing loss.

We examined the patient at age 6 weeks. Her height was 53 cm (25th centile), weight 3,700 g (10th centile), and head circumference (OFC) 37.5 cm (50th centile). She had dolichocephaly with occipital bossing, a large anterior fontanel (4 × 4 cm), and a high forehead. She had puffy eyelids and downslanting palpebral fissures with epicanthal folds. The inner canthal distance was 2.6 cm (97th centile), and outer canthal was 6.5 cm (50th centile). Her ears appeared low-set and posteri-

orly angulated, with heavy helices and antihelices. Ear length was 3.6 cm (25th–50th centiles). There was a preauricular pit on the left. Her nose was beaked with a depressed bridge. The mouth was "carp-shaped" with a thick lower lip, macroglossia, high-arched palate, and retromicrognathia (Fig. 1). The neck was short with torticollis on the right. She had a barrel-shaped chest, and a grade III/VI systolic murmur was heard over the precordium. A closed sacral dimple was noted on her back. She had thick hypertrophied labia majora and an anteriorly placed perineal fistula. Her dislocated hips were in a cast, and she had bilateral talipes equinovarus. The second toe was overriding the third toe bilaterally. All digits showed distal widening, especially of the halluces and thumbs, reminiscent of a drumstick (Fig. 2). There were whorls on the fourth and fifth fingers, and ulnar loops on the first, second, and third digits on both hands. She had head lag, was inattentive, and had hyperactive reflexes. Except for milia, her skin was normal.

Cytogenetic Studies

A peripheral blood chromosome study at about the 550 G-band level of resolution showed one normal chromosome 20 and one abnormal 20 with extra material on the q-arm (Fig. 3). Fluorescence in situ hybridization (FISH) with chromosome-specific paints (CSP) was performed using probes from Vysis (Framingham, MA) and their procedure. CSP-20 hybridized to the normal chromosome 20 and all but the distal portion of the abnormal chromosome 20 q-arm. CSP-7 hybridized to each of the normal chromosomes 7 and to the distal part of the abnormal chromosome 20 q-arm. These results suggest that the extra chromatin on the abnormal chromosome 20 was derived from a chromosome 7. Thus, the patient's karyotype was deficient for 20q13.3→20qter and duplicated for 7p15→7pter. The results of the chromosome studies of the father and mother were normal. The notation of the karyotype for the proposita was 46,XX,−20,+der(20)t(7;20)(p15;q13.3). The abnormality appeared to be a de novo mutation.

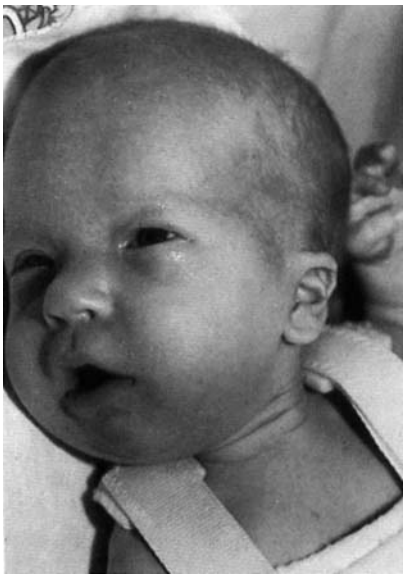

Fig. 1. Patient at age 6 weeks. Note prominent high forehead, hypertelorism, retromicrognathia, "carp-shaped" mouth, and apparently low-set, malformed ears.

Fig. 2. Patient's foot, demonstrating overriding toes and broad tips reminiscent of a drumstick.

DISCUSSION

Duplication of the distal part of 7p was present in our patient and in some others recently reported [Schmidt and Gillessen-Kaesbach, 1987; Omer et al., 1990; Delicado et al., 1991; Ramer et al., 1991; Park et al., 1993]. Although a characteristic pattern of malformation has been recognized [Milunsky et al., 1989; Zerres et al., 1989], assignment of the critical region has not been possible. To investigate this question we tabulated all cases according to their duplicated segment. We noted that most of the patients shared in common the terminal portion of 7p (Table I). In an attempt to define further the critical region we eliminated cases in which the breakpoints were not well-characterized [Eriksson et al., 1968; patient 1, Berry et al., 1979; Caspersson et al., 1971], did not include the distal segment of 7p [Šubrt et al., 1973; Miller et al., 1979; Ohdo et al., 1983; Cantú et al., 1985], or were not fully described [Roskes et al., 1990]. It is important to note that each of the reported breakpoints may not have the same degree of accuracy because of individual variation in cytogenetic analysis. However, even with this lack of precision, it is possible to group reported cases into three groups.

Fig. 3. Cytogenetic studies of patient.

TABLE I. Duplicated Segments of 7p Arranged According to Extent, and Additional Chromosomal Aberrations Involved in Each Case

Case	Authors[a]	Duplicated segment	Additional chromosomal aberrations
1	Carnevale et al. [1978]	7p11→pter	del(14)(p11→pter)
2	Zerres et al. [1989]	7p11→pter	–
3	Omer et al. [1990]	7p11→pter	del(14)(p11→pter)
4	Odell et al. [1987]	7p11.1→pter	del(11)(p15.5→pter)
5	Park et al. [1993]	7p12→pter	del(10)(p15→pter)
6	Moore et al. [1982], Pt 1	7p13→pter	del(8)(p23→pter)
7–9	Milunsky et al. [1989], Pt 1–3	7p14→pter	del(15)(q26→qter)
10	Willner et al. [1977]	7p15→pter	del(5)(p15→pter)
11	Berry et al. [1979], Pt 2	7p15→pter	del(22)(q13→qter)
12	Moore et al. [1982], Pt 2	7p15→pter	del(21)(p12→pter)
13	Schmidt and Gillessen-Kaesbach [1987]	7p15→pter	del(9)(q34→qter)
14	Gabarrón et al. [1988], Pt 1	7p15→pter	del(18)(q23→qter)
15	Delicado et al. [1991]	7p15→pter	del(7)(q36→qter)
16	Present case	7p15→pter	del(20)(q13.3→qter)
17	Ramer et al. [1991]	7p15.1→pter	del(7)(q36→qter)
18	Larson et al. [1977], Pt 2	7p21→pter	del(22)(q13→qter)
19	Rockman-Greenberg et al. [1982], Pt 1	7p21→pter	t(14;21)(p11;q11)
20–21	Gabarrón et al. [1988], Pt 2–3	7p21→pter	del(18)(p11→pter)

[a] Pt, patient number in the corresponding report.

Our study showed that the most common breakpoints, based on reported cytogenetic analysis, were 7p11, 7p15, and 7p21, and resulted in three groups of patients with duplicated segments: 7p11,12,13,14→pter, 7p15→pter, and 7p21→pter (Table II). Comparison between these groups suggested that duplication of 7p11,12,13,14→pter and duplication of 7p15→pter result in a similar phenotype. Thus, the shared region common to both groups was 7p15→pter, and it most likely contains the DNA segment responsible for this phenotype. The third group of patients with the shortest duplicated segment of 7p21→pter contained only 4 individuals, and the description of phenotypes was not complete. As a result, the critical region could not be defined further to a duplicated segment smaller than p15→pter.

In addition to the previously described phenotype associated with dup(7p) [Milunsky et al., 1989; Zerres et al., 1989] that included mental retardation, cranial defects, facial anomalies, cardiac anomalies, and joint dislocations/contractures, we have identified other findings. Gastrointestinal involvement includes imperforate anus, nonfixation of the mesenteric artery, and ascending colon, along with malrotation of the intestine and omphalocele (Table I). Also, patient 17 had severe constipation with intermittent bowel obstruction requiring recurrent hospitalization for impaction, although the pathogenesis of this was not specified in the report. Furthermore, since the findings of an abnormal mesenteric artery and ascending colon fixation were detected at autopsy only [Odell et al., 1987], it is possible that potential gastrointestinal malformations may not be clinically apparent in the reported cases and are underrepresented in the description of the phenotype. Small penis, cryptorchidism, and septation of vagina and uterus have been reported, but these defects may be difficult to detect clinically without specific evaluation. Our patient had hypertrophy of the labia majora, and a normal vagina.

Finally, our patient had a prominent high forehead which appears to contribute to the remarkable similarity in the face, as seen in the published photographs [Carnevale et al., 1978; Zerres et al., 1989; Delicado et al., 1991; Ramer et al., 1991]. Previously reported facial changes also include hypertelorism, micrognathia, and high-arched palate.

Brain malformations were found in all 5 patients with duplication (7)(p11,12,13,14→pter), while only 1 of 2 evaluated patients with duplication (7)(p15→pter) was reported to have brain anomalies. Unfortunately, information regarding brain development in the other 6 patients in the latter group was not reported, and it is not possible to determine if this problem is or is not more common in the former group.

A wide anterior fontanel was documented in 14 patients. This finding, along with delayed sutural closure seen in 7p duplication, is in contrast to the craniosynostosis (CRS) observed in patients with deletion of 7p [Schömig-Spingler et al., 1986]. One or more genes for CRS have been assigned to 7p21 (CRS1) or 7p14→p11.2 (CRS2) [Frézal and Schinzel, 1990], although the precise location is not known [Kikkawa et al., 1993; Tsuji et al., 1994]. The Saethre-Chotzen CRS gene has been located tentatively to the region between markers in 7p15→pter [Lewanda et al., 1994] or to the region around 7p21.2–7p22 [Reardon et al., 1993; Reid et al., 1993], respectively. If there is a CRS gene in 7p15→pter, then it is possible that the contrast in findings between deficiency (craniosynostosis) and duplication (open fontanel) of 7p15→pter is the result of a gene dose-effect relationship, where a single gene dose results in CRS and a triple dose in delayed closure of sutures.

In addition to dup(7)(p15→pter), our patient was deficient for 20q13.3→qter. This is the smallest terminal deletion described for the long arm of chromosome 20, and only four other reports with a similar deletion have been documented previously [Fraisse et al., 1981; Petersen et al., 1987; Porfirio et al., 1987; Shabtai et al.,

TABLE II. Manifestations of Reported Cases, Listed According to Specific Duplicated Segment of Chromosome 7p*

Trait	7p15→pter (cases 10–17)								Total	7p11,12,13,14→pter (cases 1–9): total	7p21→pter (cases 18–21): total
	9	10	11	12	13	14	15	16			
Age	4 months	9 years	8 months	5 days	2 weeks	14 months	6 months	12 years	3.2 years[j]	10 months	14 months
Mental retardation	?[i]	+	+	?	?	+	+	+	5/5	6/6	3/3
Asymmetric skull[a]	+	+	−	?	+	?	+	?	4/5	5/5	2/2
Brain anomalies	?	?	?	?	?	?	−	+	1/2	5/5[k]	1/1
Large fontanel	+	?	+	?	+	+	+	+	6/6	7/7	1/1
High forehead	?	?	?	?	?	+	+	+	3/3	3/3	1/2
Hypertelorism	+	?	+	+	?	+	+	+	6/6	7/7	2/2
Choanal/ethmoid defect[b]	+	?	?	?	+	?	−	?	2/3	3/3	?
Micrognathia	+	?	?	+	+	+	+	+	6/6	5/5	3/3
Abnormal palate[c]	+	+	?	+	+	?	+	+	6/6	4/4	3/3
Abnormal ears	+	?	+	+	+	+	+	+	7/7	9/9	3/3
Short neck	?	?	+	?	?	+	+	?	3/3	1/1	?
CVS defects[d]	?	−	+	+	+	+	+	−	5/7	8/8	1/2
GI defects[e]	?	−	−	?	?	+	+	?	2/4	3/3	1/1
GU defects[f]	?	−	−	?	+	+	+	?	3/5	4/4	?
Joint dislocation	+	?	?	?	+	?	+	?	3/3	3/3	?
Joint contraction	+	?	?	?	+	?	−	?	2/3	6/6	2/2
Broad digits[g]	?	?	+	+	?	+	+	?	4/4	4/4	1/2
Foot malformation[h]	+	?	?	+	?	?	+	+	4/4	4/4	3/3

*Case number refers to Table I. Case 15 represents the case report.
[a]Dolichocephaly, brachycephaly.
[b]Choanal stenosis, ethmoidal bony anomaly.
[c]High-arched/cleft palate.
[d]Septal defects, pulmonary stenosis, ventricular hypertrophy, dextrocardia.
[e]Malrotation, imperforate anus, nonfixed mesenteric root and ascending colon, omphalocele.
[f]Hypoplastic genitalia, septation of vagina and uterus, cryptorchidism.
[g]Broad halluces/thumbs/digits.
[h]Equinovarus, calcaneovarus, rocker-bottom feet, clubfeet.
[i]Question mark indicates that this trait was not discussed.
[j]Average age.
[k]Hydrocephalus, Dandy-Walker, aplasia of cerebellum, arhinencephaly.

1993]. No specific pattern of anomalies was recognized, although each of these patients had mental retardation, and 3 had a flat occiput and hirsutism. Our patient maintained the characteristic phenotype seen in dup(7p) in spite of deficiency for 20qter, and this was also noted in the other 7 patients with duplicated segment 7p15→pter who additionally had other segmental aneusomies. This further reinforces the idea that a syndromic phenotype is dictated by duplication of the distal region of 7p; still, a mild phenotypic variability was recognized from patient to patient which may reflect the influence of various additional monosomies. This includes arachnodactyly in case 10, hexapolydactyly and an absence of eyebrows in case 14, and kyphosis with intraspinal cyst in case 17. Awareness of the pattern of malformation of dup(7p), along with recognition of the distinct facial appearance as seen in the patients' published photographs [Carnevale et al., 1978; Delicado et al., 1991; Ramer et al., 1991; Zerres et al., 1989], may assist in further detection of this syndrome.

In summary, we describe an additional patient with duplication of 7p15→pter and analyze the reported cases. We reinforce the previously described phenotype, and add malformations of the gastrointestinal and genital systems. We restrict the critical region for this phenotype to 7p15→pter. This regional characterization is important for accurate counseling and prediction of outcome. A small duplication of 7p15→pter results in the complete phenotype, and causes the same prognosis as duplication of the whole short arm. Characterization of the responsible segment should assist in further gene mapping.

REFERENCES

Berry AC, Honeycombe J, Macoun SJR (1979): Two children with partial trisomy for 7p. J Med Genet 16:320–321.

Cantú JM, Rivas F, Ruiz C, Barajas LO, Moller M, Rivera H (1985): Trisomy 7p due to mosaic normal/dir dup(7)(p13→p22). Syndrome delineation, critical region segment assignment, and a comment on duplications. Ann Genet (Paris) 28:254–257.

Carnevale A, Frías S, del Castillo V (1978): Partial trisomy of the short arm of chromosome 7 due to a familial translocation rcp(7;14)(p11;p11). Clin Genet 14:202–206.

Caspersson T, Hultén M, Lindsten J, Zech L (1971): Chromatid interchange resulting in duplication of the short arm of chromosome number 7 in man. Ann Genet (Paris) 14:143–144.

Delicado A, Escribano E, Pajares IL, de Bustamante AD, Carrasco S (1991): A malformed child with a recombinant chromosome 7, rec(7) dup p, derived from a maternal pericentric inversion inv(7)(p15q36). J Med Genet 28:126–127.

Eriksson B, Fraccaro M, Hultén M, Lindsten J, Tiepolo L (1968): Unusual chromosomal mosaic (46,XX/46,XX,Cp+) in a girl with multiple malformations. Ann Genet (Paris) 11:6–10.

Fraisse J, Bertheas MF, Frère F, Lauras B, Rolland MO, Brizard CP (1981): Un nouveau syndrome: del(20)(q13→qter). Localisation segmentaire de gène de l'adénosine déaminase (ADA). Ann Genet (Paris) 24:216–219.

Frézal J, Schinzel A (1990): Report of the Committee on Clinical Disorders and Chromosomal Deletion Syndromes. Cytogenet Cell Genet 55:321–357.

Gabarrón J, Glover G, Jiménez A, Salas P, Pérez-Bryan J, Parra MJ (1988): Chromosomal imbalance in the offspring of translocation carriers involving 7p. Further contribution with three cases to the partial trisomy 7p phenotype. Clin Genet 33:211–219.

Kikkawa K, Narahara K, Tsuji K, Kubo T, Yokoyama Y, Seino Y (1993): Is loss of band 7p21 really critical for manifestation of craniosynostosis in 7p−? Am J Med Genet 45:108–110.

Larson LM, Wasdahl WA, Jalal SM (1977): Partial trisomy 7p associated with familial 7p;22q translocation. J Med Genet 14:258–261.

Lewanda AF, Cohen MM Jr, Jackson CE, Taylor EW, Li X, Beloff M, Day D, Clarren SK, Ortiz R, Garcia C, Hauselman E, Figueroa A, Wulfsberg E, Wilson M, Warman ML, Padwa BL, Whiteman DAH, Mulliken JB, Jabs EW (1994): Genetic heterogeneity among craniosynostosis syndromes: mapping the Saethre-Chotzen syndrome locus between D7S513 and D7S516 and exclusion of Jackson-Weiss and Crouzon syndrome loci from 7p. Genomics 19:115–119.

Miller M, Kaufman G, Reed G, Bilenker R, Schinzel A (1979): Familial, balanced insertional translocation of chromosome 7 leading to offspring with deletion and duplication of the inserted segment, 7p15→7p21. Am J Med Genet 4:323–332.

Milunsky JM, Wyandt HE, Milunsky A (1989): Emerging phenotype of duplication (7p): a report of three cases and review of the literature. Am J Med Genet 33:364–368.

Moore CM, Pfeiffer RA, Craig-Holmes AP, Scott CI Jr, Meisel-Stosiek M (1982): Partial trisomy 7p in two families resulting from different balanced translocations. Clin Genet 21:112–121.

Odell JM, Seibert JR, Bradley C, Salk D (1987): Duplication 7p in a family with t(7;11): association with anomalies of the anterior cranial base. Am J Med Genet 27:687–692.

Ohdo S, Suzumori K, Madokoro H, Sonoda T, Hayakawa K (1983): Partial trisomy for 7p due to maternal balanced translocation. Jpn J Hum Genet 28:297–300.

Omer FBS, Calzolari A, Cecconi A, Uzielli MLG (1990): Trisomy 7p: association with several craniocerebral anomalies and spongy degeneration. Pathologica 82:543–548.

Park JP, McDermet MK, Moeschler JB, Wurster-Hill DH (1993): A case of de novo translocation 7;10 and the duplication 7p, deletion 10p phenotype. Ann Genet (Paris) 36: 217–220.

Petersen MB, Tranebjaerg L, Tommerup N, Nygaard P, Edwards H (1987): New assignment of the adenosine deaminase gene locus to chromosome 20q13.11 by study of a patient with interstitial deletion 20q. J Med Genet 24:93–96.

Porfirio B, Valorani MG, Giannotti A, Sabetta G, Dallapiccola B (1987): Ring 20 chromosome phenotype. J Med Genet 24:375–377.

Ramer JC, Mowrey PN, Ladda RL (1991): Malformations in a child with dup(7pter–p15.1) and del(7q36–qter) as a result of familial pericentric inversion. Clin Genet 39:442–450.

Reardon W, McManus SP, Summers D, Winter RM (1993): Cytogenetic evidence that the Saethre-Chotzen gene maps to 7p21.2. Am J Med Genet 47:633–636.

Reid CS, McMorrow LE, McDonald-McGinn DM, Grace KJ, Ramos FJ, Zackai EH, Cohen MM Jr, Jabs EW (1993): Saethre-Chotzen syndrome with familial translocation at chromosome 7p22. Am J Med Genet 47:637–639.

Rockman-Greenberg C, Ray M, Evans JA, Canning N, Hamerton JL (1982): Homozygous Robertsonian translocations in a fetus with 44 chromosomes. Hum Genet 61:181–184.

Roskes EJ, Boughman JA, Schwartz S, Cohen MM (1990): Congenital cardiovascular malformations (CCVM) and structural chromosome abnormalities: a report of 9 cases and literature review. Clin Genet 38:198–210.

Schmidt A, Gillessen-Kaesbach G (1987): Duplication 7p. A problem in karyotype-phenotype correlation. Ann Univ Sarav Med [Suppl] 7:271–272.

Schömig-Spingler M, Schmid M, Brosi W, Grimm T (1986): Chromosome 7 short arm deletion, 7p21→pter. Hum Genet 74:323–325.

Shabtai F, Ben-Sasson E, Arieli S, Grinblat J (1993): Chromosome 20 long arm deletion in an elderly malformed man. J Med Genet 30: 171–173.

Šubrt I, Kozák J, Hniková O (1973): Microdensitometric identification of the pericentric inversion of chromosome no. 2 and of duplication of the short arm of chromosome no. 7 in a reexamined case. Hum Hered 23:331–337.

Tsuji K, Narahara K, Kikkawa K, Murakami M, Yokoyama Y, Ninomiya S, Seino Y (1994): Craniosynostosis and hemizygosity for D7S135 caused by a de novo and apparently balanced t(6;7) translocation. Am J Med Genet 49:98–102.

Willner JP, Paciuc S, Cristian S, Hsu LYF, Murphy R, Hirschhorn K (1977): The 7p partial trisomy syndrome. Pediatr Res 11:530 (abstract).

Zerres K, Schwanitz G, Gellissen K, Schroers L, Sohler R (1989): Duplication 7p de novo and literature review. Ann Genet (Paris) 32:225–229.